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A Novel Method for the Degradation of the Carbon Chain of Organic Acids and Their Derivatives

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A Novel Method for the Degradation of the Carbon Chain of Organic Acids and Their Derivatives

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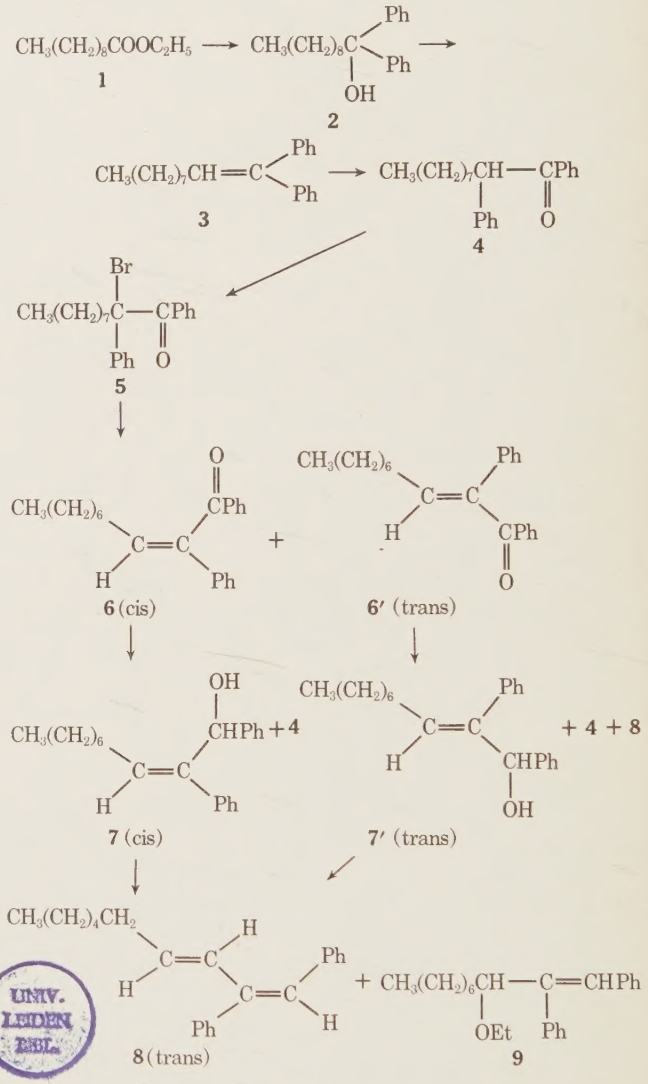
A convenient scheme for the stepwise degradation of ethyl caprinate (**1**) is described, which allows the removal of either one, two, or three carbon fragments from the chain, affording high yields of the corresponding carbonyl compounds. The method may have important applications in the transformations of steroids, lipids, and other natural products.

The utility of side chain degradative schemes in the syntheses, modification, and structural elucidation of natural products is well known.[2] The same type of reactions also find useful applications in the transformations of lipids.[3] However, none of the available methods[4-8] for degrading carboxylic acids give particularly attractive yields.

Furthermore, to our best knowledge, there is no satisfactory degradative scheme which permits the elimination of two carbon atoms at a time. The present paper describes a practical and flexible procedure for removing one, two, or three carbon atoms. The key step makes use of a rearrangement worked out before[9] and found to be successful on a variety of substrates, including some steroids. The individual steps in the degradative sequence are outlined in Scheme I.

SCHEME I



Results and Discussion

A commericial sample[10] of pure (99% by glc) ethyl caprinate (**1**) was allowed to react with an ether solution of phenylmagnesium bromide, prepared in the usual way. After purification of the crude alcohol by column chromatography, a nearly quantitative yield (96%) of 1,1-diphenyl-1-decanol (**2**) was obtained. Dehydration of the alconol was achieved in refluxing acetic anhydride. After suitable work-up and purification of the crude product by column chromatography, a sufficiently pure sample of 1,1-diphenyl-1-decene (**3**) was obtained. The yield based on the ester **1** was 85%. The identity of the product was confirmed by infrared and nmr spectroscopy and by elemental analysis.

The olefin **3** was without any further purification subjected to the conditions of the Kakis reaction,[9] which converted it smoothly to 1,2-diphenyl-1-decanone (**4**).

After purification of the crude product by recrystallization from methanol followed by thin layer chromatography, a 90% yield (76.5% overall) of pure (mp 56.5–57°) ketone **4** was obtained. The identity of the ketone was established by infrared, ultraviolet, and nmr spectroscopy and by elemental analysis.

The following two steps in the degradation sequence involved the α-bromination[11] of 1,2-diphenyl-1-decanone **4** followed by the collidine dehydrobromination[12] of the resulting 1,2-diphenyl-2-bromo-1-decanone (**5**).

Both reactions were nearly quantitative. The identity of the products was in each case confirmed by infrared and nmr spectroscopy. The ketones **6** and **6′** were further identified by elemental analysis.

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As expected, the collidine dehydrobromination of **5** produced a mixture of cis (**6**) and trans (**6′**) α,β-unsaturated ketones which were separated by thin layer chromatography on fluorescent silica plates and characterized by nmr.[13] The ratio of cis to trans product was about 1:1.6.

The reduction of the isomeric ketones **6** and **6′** was accomplished by means of the specialized reagent[14] $AlNa(OCH_3OCH_2CH_3)_2H_2$, producing the allylic alcohols **7** and **7′**, respectively. After purification by thin layer chromatography a 75% yield of the cis (**7**) and a 50% yield of the trans (**7′**) alcohol was obtained. Thus the combined yield of alcohols was 62.5% (48% overall, *i.e.*, based on **1**).

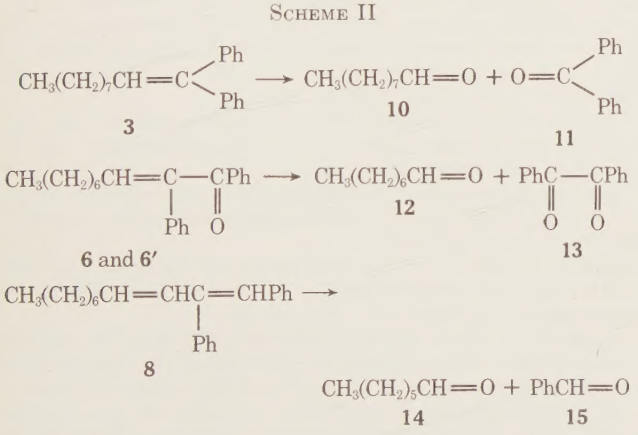
A small quantity (*ca.* 6%) of the ketone **4** was also isolated, presumably stemming from 1,4 reduction of the conjugated ketones **6** and **6′**.

The three components were readily separable by thin layer chromatography.

The alcohols **7** and **7′** were subsequently dehydrated with ethanolic hydrochloric acid.[15] Thus a 70% (34% overall) yield of 1,2-diphenyl-1,3-decadiene (**8**) was obtained whose nmr spectrum was compatible with the trans,trans structure shown. In addition a 20% yield of 1,2-diphenyl-3-ethoxy-1-decene (**9**) was isolated. Attempting to minimize the formation of this side product, the dehydration of the alcohols **7** and **7′** was also tried with methanol and isopropyl alcohol solvents. However, the yields were in these cases substantially lower than those obtained from the ethanolic hydrochloric acid dehydration.

Thus it can be seen that the sequence of reactions described above and summarized in Scheme I generates compounds **3**, **6** and **6′**, and **8**, which can in turn be degrated by ozonolysis with the corresponding loss of one, two, and three carbon fragments, respectively. These possibilities are summarized in Scheme II.

SCHEME II



We have in fact carried out the ozonolysis of these compounds by standard procedures[16] and have isolated and identified all the fragments. Thus the ozonolysis of 1,1-diphenyl-1-decene (**3**) resulted in the formation of nonanal (**10**) and benzophenone (**11**). Similarly compounds **6** and **6′** yield octanal (**12**) and benzil (**13**) and compound **8** yields heptanal (**14**) and benzaldehyde (**15**). To facilitate the separation and identification of the ozonolysis products the mixtures were treated with the Wanzlick reagent,[17] which selectively converts the aldehydes into crystalline derivatives. These derivatives were easily separable by chromatography, and their melting points were in agreement with those reported in the literature.[17] Furthermore, mixture melting points with authentic samples showed no depression. In the case of heptanal and benzaldehyde additional confirmation was obtained by glc and by preparing the 2,4-dinitrophenylhydrazone derivatives. Again the melting points were in agreement with those reported in the literature.

We estimate that the typical ozonolysis yields were about 80%. Thus we have achieved a two-carbon fragment degradation with an overall yield of 60% for the six-step process.

The corresponding overall yield for the removal of three carbon atoms was about 28% for the eight-step process.

The removal of one carbon atom from the chain involves three steps and proceeds with an overall yield of about 70%.

In view of the above, we feel that the procedure we have developed is superior to the existing degradative schemes, not only because of the higher yields but also because in most cases substantial portions of unchanged starting materials can be easily recovered. Thus the process lends itself well to recycling, which may be significant in industrial terms.

From the foregoing discussion, it can be concluded that a useful degradative method has been developed with potential important applications in the chemistry of natural products. This possibility is currently under investigation.

Experimental Section

General.—Melting points were taken on a Köfler apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 257 spectrophotometer. Ultraviolet spectra were recorded on a Beckman Model DK2A spectrophotometer. Nmr spectra were determined on a Jeol Model C60H spectrometer using tetramethylsilane as internal standard and are reported in parts per million. Gas chromatographic analysis was carried out on a Loenco Model 160 gas chromatograph equipped with a LAC 446, 8-ft column. Microanalysis were performed by the microanalysis service of C. N. R. S. at the Gif Sur Yvette laboratories in France.

1,1-Diphenyl-1-decanol (2).—The preparation of this compound involved the standard addition of phenylmagnesium bromide (0.5 mol) to a commercial sample[10] of ethyl caprinate (**1**) (10 g, 0.05 mol, 99% pure).

After hydrolysis of the reaction mixture and decomposition with a saturated solution of ammonium chloride, *ca.* 20.3 g of crude product was obtained (yellow oil).

After purification by column chromatography over silica (Merck, 0.05–0.2 mm) using a pentane–ether mixture as the eluent (10:1), 15 g of the pure alcohol (96%) was obtained.

1,1-Diphenyl-1-decene (3).—This compound was prepared by dehydrating a sample of the alcohol **2** (15 g) in refluxing acetic anhydride for a period of 10 hr. After removal of the solvents by rotatory evaporation, the crude product was purified by column chromatography over silica (Merck, 0.05–0.2 mm) using petroleum ether (bp 48–55°) as the eluent. Thus 12.4 g (85%) of pure 1,1-diphenyl-1-decene was obtained. The sample showed the following physical data: ir (CCl_2=CCl_2) 3080, 3060, 3020, 1600, and 700 cm^{-1}; nmr ($CDCl_3$) δ 0.88 (3 H, multiplet,

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methyl), 1.28 (12 H, singlet, $-CH_2-$), 2.1 (2 H, multiplet, $-CH_2$ allylic), 6.09 (1 H, triplet, ethylenic, J = 7.5 Hz), 7.23 (10 H, aromatic protons).

The above nmr constants were in agreement with those reported in the literature.[18]

Anal. Calcd for $C_{22}H_{28}$: C, 90.35; H, 9.65. Found: C, 90.37; H, 9.46.

1,2-Diphenyl-1-decanone (4).—A sample (2 g) of the olefin **3** was converted to 1,2-diphenyl-1-decanone (**4**) by the Kakis method.[9] The crude product (2.4 g) was then purified by recrystallization from methanol, followed by thin layer chromatography of the mother liquors over fluorescent silica using a petroleum ether–ether mixture (6:1) as the eluent. Thus 1.9 g (90%) of pure (mp 56.5–57°) 1,2-diphenyl-1-decanone (**4**) was obtained. Confirmation of structure was obtained by the following physical data: ir (CCl_4) 3090, 3070, 3030, 1690, 1450, and 690 cm^{-1}; nmr ($CDCl_3$) δ 0.85 (3 H, multiplet, $-CH_3$), 1.25 and 2 [14 H, singlet, $(-CH_2)_7$], 4.53 (1 H, triplet, H α to ketone, J = 7.5 Hz), 7.25–8.1 (10 H, aromatic protons); uv (95% EtOH) 244 mμ (ϵ 11,180).

Anal. Calcd for $C_{22}H_{28}O$: C, 85.66; H, 9.15; O, 5.19. Found: C, 85.38; H, 8.98; O, 5.39.

1,2-Diphenyl-2-bromo-1-decanone (5).—A sample (1 g) of the ketone **4** was brominated by the method of Baudry.[11] After work-up 1.23 g (99%) of chromatographically pure product was obtained: ir (CCl_4) 3090, 3070, 3030, 1685, 1450, 1225, doublet at 695–685, and 655 cm^{-1}; nmr ($CDCl_3$) δ 0.85 (3 H, multiplet, $-CH_3$), 1.2 [12 H, multiplet, $(-CH_2)_6$], 2.4 (2 H, multiplet, $-CH_2CBrPh$), 7.15–7.85 (10 H, aromatic protons).

***cis*- and *trans*-1,2-Diphenyl-1-keto-2-decene (6 and 6′).**—Dehydrobromination of a sample (1.25 g) of compound **5** by collidine[12] afforded a mixture (0.92 g, 99%) of *cis*- and *trans*-1,2-diphenyl-1-keto-2-decene. Analytical thin layer chromatography of the mixture on silica–silver nitrate (7%) plates with petroleum ether–ether (30:1) eluent showed that it was practically pure.

Separation was achieved on fluorescent silica preparatory plates by multiple elutions with the above solvent mixture (R_f of trans compound **6**, R_f of cis compound **4**).

Thus 330 mg of the pure cis isomer **6** and 530 mg of the pure trans isomer **6′** were obtained: ir (CCl_2CCl_2) 3090, 3070, 3030, 1675, 1600, 1450, 1215, and 690 cm^{-1}; nmr ($CDCl_3$) for trans compound δ 0.85 (3 H, multiplet, $-CH_3$), 1.25 [10 H, multiplet, $(-CH_2)_5$], 2.1 (2 H, multiplet, $-CH_2-$ allylic), 6.28 (1 H, triplet, ethylenic, J = 7.5 Hz), 7.25–8.2 (10 H, aromatic protons); for cis compound δ 0.87 (3 H, multiplet, $-CH_3$), 1.27 [10 H, multiplet, $(-CH_2-)_5$], 2.25 (2 H, multiplet, $-CH_2-$ allylic), 6.5 (1 H, triplet, ethylenic, J = 7.5 Hz), 7.2–8 (10 H, aromatic protons); uv (95% EtOH) for cis 245 mμ (ϵ 18,900); for trans 245 mμ (ϵ 24,000).

Anal. Calcd for $C_{22}H_{26}O$: C, 86.23; H, 8.55; O, 5.22. Found for cis: C, 86.28; H, 8.77; O, 5.40. Found for trans: C, 86.40; H, 8.52; O, 5.45.

1,2-Diphenyl-2-decen-1-ol (7 and 7′). A. Reduction of Compound 6.—A sample of compound **6** (250 mg) was reduced with bis(2-methoxyethoxy)sodium aluminum hydride, $AlNa(OCH_3OCH_2CH_3)_2H_2$, by a procedure similar to that of Bazant, *et al.*[14] On work-up 250 mg of crude product was obtained. Separation was achieved by thin layer chromatography on fluorescent silica plates with a petroleum ether–ether mixture (5:1) as the eluent. Thus 190 mg (75%) of the pure alcohol **7** was obtained. The chromatography also afforded 20 mg of ketone **4**. **7** had ir ($CCl_2=CCl_2$) 3620, 3080, 3030, 1600, 1490, 1450, and 700 cm^{-1}; nmr ($CDCl_3$) δ 0.87 (3 H, multiplet, $-CH_3$), 1.23 [10 H, $(-CH_2-)_5$], 1.95 (2 H, multiplet, $-CH_2-$ allylic), 5.45 (1 H, singlet, –CHOH), 5.92 (1 H, triplet, ethylenic H, J = 7.5 Hz), 7.1–7.2 (10 H, aromatic protons).

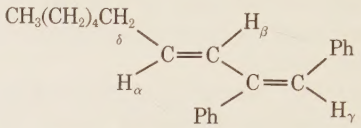
Anal. Calcd for $C_{22}H_{28}O$: C, 85.66; H, 9.15; O, 5.19. Found: C, 85.68; H, 9.19; O, 5.20.

B. Reduction of Compound 6′.—A reduction of a sample (500 mg) of compound **6′** by a procedure identical with the above afforded 440 mg of a crude product. The purification of the product mixture and separation of the components was carried out as before. Thus 250 mg (50%) of alcohol **7′**, 30 mg of ketone **4**, and 20 mg of the dehydration product 1,2-diphenyl-1,3-decadiene (**8**) were obtained in a pure state. **8** had ir same as **7**; nmr ($CDCl_3$) δ 0.9 (3 H, multiplet, $-CH_3$), 1.35 [10 H, $(-CH_2-)_5$], 2.25 (3 H, multiplet, allylic $-CH_2-$ and –OH), 5.88 (2 H, triplet, 6:3:1, –CHOH and CH=), 7.1–7.3 (10 H, aromatic protons).

Anal. Calcd for $C_{22}H_{28}O$: C, 85.66; H, 9.15; O, 5.19. Found: C, 85.95; H, 9.28; O, 5.14.

1,2-Diphenyl-1,3-decadiene (8).—Dehydration of either alcohol **7** or **7′** (200 mg) by means of ethanolic hydrochloric acid[15] gave after work-up a mixture of two products (200 mg). The mixture was separated on fluorescent silica plates with a mixture of petroleum ether–ether (20:1) as the eluent.

Thus 130 mg (70%) of pure diene **8** (R_f 9) and 45 mg (20%) of 1,2-diphenyl-3-ethoxy-1-decene (**9**) (R_f 7.5) were obtained. Diene **8** had ir ($CCl_2=CCl_2$), 3090, 3070, 3030, 1600, 1490, 1470, 1450, and 700 cm^{-1}; nmr ($CDCl_3$) δ 0.88 (3 H, multiplet, $-CH_3$),



1.3 [8 H, $(-CH_2-)_4$], 2.1 (2 H, multiplet, $-CH_2-$ allylic), two triplets centered at 5.27 (H_α, $J_{\alpha,\delta}$ = 7.5, $J_{\alpha,\beta}$ = 16 Hz); 6.36 (H_β, doublet, $J_{\alpha,\beta}$ = 16 Hz), 6.42 (H_α, singlet), 6.65–7.5 (10 H, aromatic protons).

Anal. Calcd for $C_{22}H_{26}$: C, 90.98; H, 9.02. Found: C, 90.84; H, 9.14.

Compound **9** had ir (CS_2) 3080, 3060, 3030, 1080, 760, and 700 cm^{-1}; nmr ($CDCl_3$) δ 0.88 (3 H, multiplet, $-CH_3$), 1.05–1.7 [12 H, large, $(-CH_2-)_6$ and triplet due to $-CH_3$ of CH_3CH_2O-], quadruplet centered at 3.65 due to $-CH_2-$ of $-OCH_2CH_3$, 3.9 (1 H, –CHOEt), 6.7 (1 H, singlet, RC=CH–), 7–7.6 (10 H, aromatic protons).

Ozonolysis.—All of the ozonolysis reactions were carried out as follows. The reactants were dissolved in a mixture of methanol and methylene chloride (2:3). The solution was then ozonized until the appearance of a blue color (5–10 min).

Decomposition was accomplished by stirring the product mixture with a solution of potassium iodide in glacial acetic acid.

The mixtures were then extracted with ether and the organic phase was decolorized by washing with a sodium thiosulfate solution and a saturated sodium bicarbonate solution.

The combined ether extracts were then dried over anhydrous magnesium and sodium sulfates.

Removal of the solvents by rotatory evaporation afforded the crude mixtures of the ozonolysis products. In some instance direct chromatographic separation of these products proved difficult. Consequently, the mixtures were treated with freshly prepared Wanzlick reagent,[17] which converted all the aldehyde components of the mixtures to the crystalline dianilinoethane derivatives, easily separable by chromatography. Purification was achieved by recrystallization from methanol.

Thus from the ozonolysis of 1,1-diphenyl-1-decene (**3**), nonanal (**10**) was isolated as the dianilinoethane derivative (mp 54–55°) along with benzophenone (mp 46.5–48°).

Similarly the ozonolysis of 1,2-diphenyl-1-keto-2-decenes (**6** and **6′**) afforded octnal **12** as the dianilinoethane derivative (mp 53.5–54.5°) and benzil **13** (mp 95–96°).

Finally the dianilinoethane derivatives of heptanal (**14**) (mp 77–78°) and benzaldehyde (mp 136–137°) were isolated from the ozonolysis of 1,2-diphenyl-1,3-decanone (**8**).

In all of the above cases the observed melting points were in agreement with those reported in the literature.[17] Confirmation was obtained by mixture melting points with authentic samples.

In the last ozonolysis additional confirmation was obtained by gas chromatography of the original mixture against known standards.

Registry No.—**1**, 110-38-3; **2**, 21236-83-9; **3**, 1530-27-4; **4**, 38821-25-9; **5**, 38821-26-0; **6**, 38821-29-3; **6′**, 38821-30-6; **7**, 38896-72-9; **7′**, 38896-73-0; **8**, 38821-31-7; **9**, 38821-28-2.

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Steroids Derived from Bile Acids. A Novel Side-Chain Degradation Scheme

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Steroids Derived from Bile Acids. A Novel Side-Chain Degradation Scheme

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A four-step degradative sequence of methyl cholanate (1) and methyl lithocholate (**13**) is described with a 35 and 27% overall yield, respectively. The method involves conversion of the esters to the rearranged phenyl ketones (**4** and **16**) which are in turn subjected to a Norrish type II photoelimination. Ozonolysis of the final products leads to physiologically important steroid compounds.

In a recent publication[1] we have described a novel method for the degradation of the carbon chain of organic acids and their derivatives. The key substance in the sequence we have described is a phenyl ketone which is easily obtainable by an established[2] rearrangement procedure. In view of the intensive recent interest[3-7] in the photolysis of such compounds by Norrish type II processes, we have decided to utilize this reaction, combine it with a part of our previous scheme, and apply it to the degradation of the side chain of steroidal substrates. Thus a convenient modification of the original degradative sequence has resulted, the individual steps of which are outlined in Scheme I.

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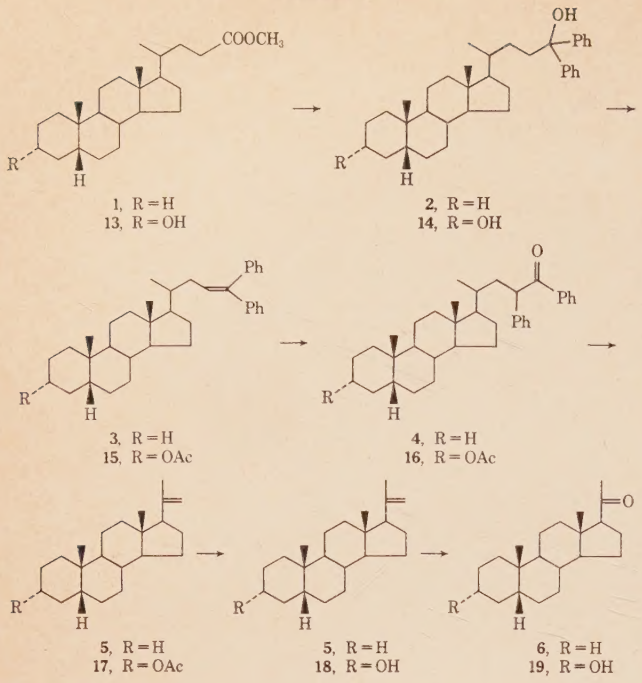
Results and Discussion

Samples of esters **1** and **13** were converted to the corresponding tertiary alcohols **2** and **14** by means of a standard Grignard reaction with phenylmagnesium bromide in nearly quantitative yields. Dehydration of the alcohols in acetic anhydride afforded the corresponding olefins **3** and **15**. The yields for this step were 85%. The olefins **3** and **15** were easily and quantitatively converted to the corresponding ketones **4** and **16** by means of the Kakis reaction.[2] This reaction in the present system generates a pair of diastereomers, epimeric around the C_{23} asymmetric carbon. Although not directly related to the degradative scheme, which utilizes the mixture, we thought it would be of theoretical as well as practical interest to separate the stereoisomers and to obtain the spectra and their physical constants. This seemed to be particularly appropriate since these compounds have never been prepared before and their physiological properties are not known. Separation was achieved by laborious thin-layer chromatography. The pure isomers were isolated and their melting points, optical rotations, and nmr spectra were obtained.

SCHEME I



The mixtures of ketones **4** and **16** were subjected to the conditions of the Norrish type II photoelimination, which resulted in a complex mixture of products. Separation of the mixtures by thin-layer chromatography afforded the degradation products **5** and **17** in 45 and 35% yields, respectively. No attempt was made to isolate or identify the other photolysis products.

We have found by means of repeated trials that a small increase in the yields occurs when the photolysis is carried out in *tert*-butyl alcohol instead of benzene.

Identification of structure was obtained by infrared and nuclear magnetic resonance spectroscopy and by elemental analysis. To obtain final confirmation, samples of compounds **5** and **18** were subjected to standard ozonolysis and the corresponding ketones **6** and **19** were compared and found to be identical with authentic samples. An authentic sample of compound **19** was obtained commercially.[8] The other authentic sample, compound **6**, was synthesized from pregnenolone (**7**) *via* a five-step synthesis, the details of which are shown in Scheme II.

The degradative scheme (I) described above afforded a 35 and 27% overall yield for the four-step degradation of methyl cholanate and methyl lithocholate, respectively. These yields are significantly higher than those obtained by many other published pathways.[9-14] We are currently investigating its application to the degradation of the lanosterol side chain and other steroidal substrates. Finally, it is noteworthy that the terminal products of our pathway are useful precursors of physiologically important compounds.[15]

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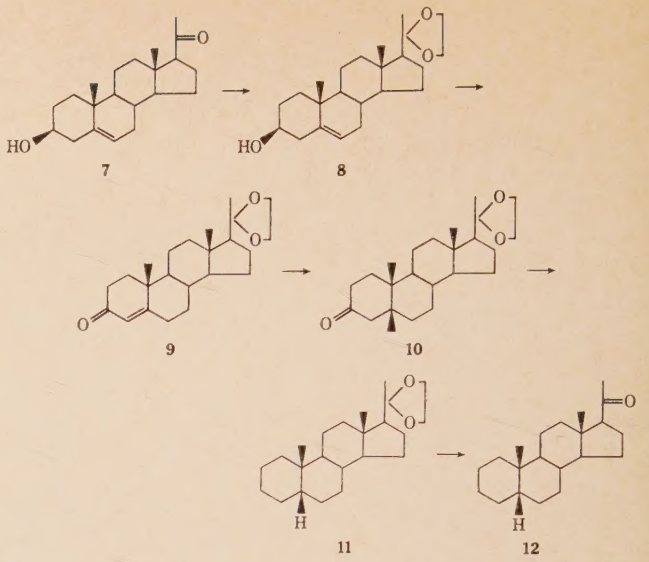
SCHEME II



Experimental Section

General.—Melting points were taken on a Kofler apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 257 spectrophotometer. Nmr spectra were determined on a Joel Model C60H spectrometer using tetramethylsilane as internal standard and are reported in parts per million. Optical rotations were measured with the aid of a Perkin-Elmer Model 141 polarimeter. Irradiations were performed with a Hanau TQ 150-W medium-pressure mercury lamp contained in a quartz immersion well. The 3130-Å line was isolated with a 1-cm path of 0.002 *M* potassium chromate in a 5% aqueous solution of potassium carbonate. The required cooling was achieved by circulation of this solution. Microanalysis were performed by the microanalysis service of CNRS at the Gif Sur Yvette Laboratories in France.

24,24-Diphenyl-24-hydroxy-5β-cholane (2).—This compound was prepared from a sample (17 g, 0.0227 mol) of pure (mp 87–88°) methyl cholanate (**1**) by the standard addition of phenylmagnesium bromide (57.8 g, 0.227 mol) in anhydrous ether. After hydrolysis of the reaction mixture and decomposition with a saturated solution of ammonium chloride, a viscous yellow oil (27 g) was obtained. After purification by column chromatography over silica (Merck 0.05–0.2 mm) using a pentane–ether mixture as the eluent (10:1), 21.9 g of alcohol **2** were obtained. The crystallization from hexane (−10°) afforded a pure (mp 95–96°) product in 96% yield: ir (CCl_2CCl_2) 3610, 3080, 3060, 3030, and 700 cm^{-1}; nmr ($CDCl_3$) 0.62, 0.89 (3 H, singlet, C_{18} and C_{19} protons), 7.1–7.6 (10 H, multiplet, aromatic protons).

Anal. Calcd for $C_{36}H_{50}O$: C, 86.69; H, 10.11; O, 3.21. Found: C, 86.47; H, 9.97; O, 3.28.

24,24-Diphenyl-5β-chol-23-ene (3).—This compound was prepared by dehydrating a sample of alcohol **2** (8.8 g) in refluxing acetic anhydride for a period of 12 hr. After removal of the solvents by rotatory evaporation and one recrystallization from methanol–ether, a crystalline sample (8.2 g) was obtained. Further purification was achieved by column chromatography over silica (Merck, 0.05–0.2 mm) using pentane as the eluent. Thus a pure (mp 120–122°) sample (7.1 g, 84%) of olefin **3** was obtained: ir (CCl_2CCl_2) 3080, 3060, 3020, 1600, and 700 cm^{-1}; nmr ($CDCl_3$) δ 0.61, 0.9 (singlet, C_{18} and C_{19} protons), 6.1 (1 H, triplet, ethylenic, J = 7.5 Hz), 7–7.6 (10 H, multiplet, aromatic protons).

Anal. Calcd for $C_{36}H_{48}$: C, 89.94; H, 10.06. Found: C, 89.77; H, 10.03.

23,24-Diphenyl-5β-cholan-24-one (4).—A sample (1.3 g) of olefin **3** was converted to ketone **4** by the Kakis method.[2] The reaction afforded 1.27 g (94%) of sufficiently pure ketone **4**: ir (CCl_2CCl_2) 3090, 3060, 3030, 1690, 1600, 1450, and 700 cm^{-1}.

Anal. Calcd for $C_{36}H_{48}O$: C, 87.04; H, 9.74; O, 3.22. Found: C, 86.74; H, 9.45; O, 3.24.

This reaction results in a mixture of two (**4a** and **4b**) diastereomers, epimeric around the C_{23} asymmetric carbon. The stereoisomers were separated by thin-layer chromatography on fluores-

cent silica using several successive elutions with pentane–ether (50:1). Subsequently, each isomer was recrystallized from methanol. The least polar substance (**4a**) melted sharply at 146–146.5°. The other isomer (**4b**) melted sharply at 158–159°: nmr (**4a**) ($CDCl_3$) δ 0.6, 0.9 (singlets, C_{18} and C_{19} protons), 4.77 (multiplet, 1 H, proton α to the carbonyl), 7.05–8.2 (10 H, multiplet, aromatic protons); nmr (**4b**) 0.47, 0.87 (singlets, C_{18} and C_{19} protons), 4.65 (multiplet, 1 H, proton α to the carbonyl), 7.1–8.2 (10 H, multiplet, aromatic protons); $[\alpha]D$ ($CHCl_3$) (**4a**) −73°, $[\alpha]D$ ($CHCl_3$) (**4b**) +96.5°.

20-Methylene-5β-pregnane (5).—A sample (1 g) of the diastereomeric mixture of ketones (**4**) was dissolved in anhydrous *tert*-butyl alcohol (70 ml) and irradiated for a period of 3 hr. On evaporation of the solvents under vacuum, a sample (1.03 g) of crude (yellow oil) product was obtained. Purification was achieved by thin-layer chromatography on silica containing 8% silver nitrate. After three elutions with pentane–ether (40:1) a pure sample (275 mg; *ca.* 45%; R_f 0.7) of olefin **5** was obtained which crystallized spontaneously. Recrystallization was achieved with some difficulty from methanol–ether producing the analytical sample (mp 72–74°): ir (CS_2) 3080 and 885 cm^{-1}; nmr ($CDCl_3$) δ 0.57, 0.95, 1.77 (singlets, C_{18}, C_{19}, and C_{21} protons), 4.7, 4.85 (2 H, two adjacent singlets, exocyclic methylene protons); $[\alpha]D$ ($CHCl_3$) +12.5°.

Anal. Calcd for $C_{22}H_{36}$: C, 87.92; H, 12.08. Found: C, 87.53; H, 12.02.

The above irradiation was repeated many times. The yields in *tert*-butyl alcohol ranged from 45 to 48% and in benzene from 35 to 40%.

Pregnenolone Ethylene Ketal (8).—A commercial sample (29 g, 0.091 mol) of pregnenolone (**7**) was converted to the ethylene ketal (**8**) by a standard method.[16] Thus 31 g (95%) of crude product was obtained. After recrystallization from methanol containing a few drops of pyridine a pure sample of ketal **8** was obtained which melted at 164–166° in agreement with the literature:[16] ir (CS_2) 3610, 1070, 1050, 1025, and 950 cm^{-1}; nmr ($CDCl_3$) δ 0.81 (3 H, singlet, C_{18} protons), 1.05 (3 H, singlet, C_{19} protons), 1.33 (3 H, singlet, C_{21} protons), 3.5 (1 H, C_3 proton), 3.93 (4 H, multiplet, $-OCH_2CH_2O-$), 5.37 (1 H, multiplet, ethylenic proton).

Progesterone 20-Ethylene Ketal (9).—A sample of pregnenolone ethylene ketal (**8**) above (15.6 g, 0.044 mol) was converted by a standard Oppenauer oxidation to progesterone ethylene ketal (**9**). The yield of the crude product (13.9 g) was 89%. Recrystallization from methanol containing a few drops of pyridine afforded a pure product (mp 189–191°) whose melting point was in agreement with the literature value:[16] ir (CS_2) 1680, 1070, 1050, and 950 cm^{-1}; nmr ($CDCl_3$) δ 0.71 (3 H, singlet, C_{18} protons), 1.2 (3 H, singlet, C_{19} protons), 1.3 (3 H, singlet, C_{21} protons), 3.9 (4 H, multiplet, $-CH_2CH_2O-$), 5.7 (1 H, singlet, C_4 proton).

20-Ethylenedioxy-5β-pregnane-3-one (10).—This compound was prepared by an adaptation of a previously reported method.[17] Thus a sample of progesterone ethylene ketal (**9**) (5 g, *ca.* 0.014 mol) in freshly distilled *N*-methylpyrrolidine (250 ml) was treated with a commercial sample[18] (2.5 g, 5% Pd on $CaCO_3$) of the catalyst and hydrogenated. At the end of the reaction a white crystalline product (5.1 g) was isolated which consisted of a mixture of the two stereoisomers with the 5β isomer predominating. On recrystallization from acetone containing a few drops of pyridine a pure sample (2.7 g, mp 172–174°) of the 5β isomer was obtained. Column chromatography of the mother liquors over silica (Merck 0.05–0.2 mm) with pentane–ether (1:1) afforded an additional sample (1.55 g) of the pure 5β isomer (total yield ~80%): ir (CS_2) 1715, 1070, 1050, and 950 cm^{-1}; nmr ($CDCl_3$) δ 0.77 (3 H, singlet, C_{19} protons), 0.9 (3 H, singlet, C_{18} protons), 1.32 (3 H, singlet, C_{21} protons), 3.57 (4 H, multiplet, $-OCH_2CH_2O-$). Final confirmation of the structure of **10** was obtained by hydrolysis of a small sample which afforded 5β-pregnane-3,20-dione whose melting point (123–124°) and spectra were in agreement with previously reported values.[19]

20-Ethylenedioxy-5β-pregnane (11).—This compound was prepared by a standard Wolff–Kishner reduction of a sample (2.8 g, *ca.* 0.008 mol) of compound **10**. Thus a white crystalline product (2.6 g, 95%) was obtained, and recrystallized from acetone containing a few drops of pyridine. The pure sample melted at 110–112°: ir (CS_2) 1070, 1050, and 950 cm^{-1}; nmr ($CDCl_3$) δ 0.72 (3 H, singlet, C_{19} protons), 0.9 (3 H, singlet, C_{18} protons), 2.3 (broad band, methylenes, and C_{21} methyl protons), 3.9 (4 H, multiplet, $-OCH_2CH_2O-$).

5β-Pregnan-20-one (12). A.—A sample of ethylene ketal **11** (2.6 g) was hydrolyzed in acetic acid–water (1:1, 100 ml) for a period of 3 hr. To increase the solubility it was necessary to add some methylene chloride. At the end of the reaction the mixture was neutralized with concentrated ammonium hydroxide, diluted with water, and extracted with methylene chloride. On drying the extracts and evaporation of the solvent, a crude crystalline product (2.5 g) was obtained. After recrystallization in ethanol a pure sample (mp 114–116°) of ketone **12** was obtained: ir (CS_2) 1705 cm^{-1}; nmr ($CDCl_3$) δ 0.6 (3 H, singlet, C_{18} protons), 0.92 (3 H, singlet, C_{19} protons), 2.1 (3 H, singlet, C_{21} protons). The above physical constants were in complete agreement with previously reported values.[15]

B.—To obtain final confirmation of compound **5** a small sample was subjected to ozonolysis in the usual way. This afforded a keto steroid whose melting point and ir and nmr spectra were identical with those of the authentic sample of 5β-pregnan-20-one (**12**) independently prepared above. When mixture melting points were taken there was no temperature depression.

3α,24-Dihydroxy-24,24-diphenyl-5β-cholane (14).—This compound was prepared by a standard Grignard reaction in tetrahydrofuran. The procedure was identical with that reported above for compound **2**. Thus starting with a sample (25 g) of methyl lithocholate (**13**) we have obtained 31.15 g (95%) of pure (mp 146–147°) diol **14**: ir (CS_2) 3610, 3090, 3060, 3040, and 700 cm^{-1}; nmr ($CDCl_3$) δ 0.6, 0.9 (singlets, C_{18} and C_{19} protons), 3.52 (1 H, multiplet, 3β H), 7.1–7.6 (10 H, multiplet, olefinic protons).

3α-Acetoxy-24,24-diphenyl-5β-chol-23-ene (15).—Simultaneous acetylation of the 3-hydroxy and dehydration of the Grignard product **14** was achieved by refluxing a sample (24 g) of diol **14** with acetic anhydride–acetic acid (145 ml, 5:1) for a period of 5 hr. Upon the usual work-up and recrystallization from methanol–methylene chloride a pure sample (mp 161–163°, 85%) of compound **15** was obtained. The observed melting point was in agreement with that reported in the literature:[20] ir (CS_2) 3080, 3060, 3020, 1740, 1240 and 700 cm^{-1}; nmr ($CDCl_3$) δ 0.62, 0.93 (singlets, C_{18} and C_{19} protons), 2.0 (singlet, acetoxy protons), 4.72 (1 H, multiplet, 3β proton), 6.1 (1 H, triplet, ethylenic proton, J = 7.5 Hz), 7–7.5 (10 H, multiplet, aromatic protons).

3α-Acetoxy-23,24-diphenyl-5β-cholan-24-one (16).—This product was obtained from a sample of olefin **15** (5 g) by means of the Kakis method.[2] The reaction afforded 4.9 g (95%) of sufficiently pure ketone **16**: ir (CS_2) 3080, 3060, 3030, 1735, 1685, 1240, and 700 cm^{-1}.

Anal. Calcd for $C_{38}H_{50}O_3$: C, 82.26; H, 9.08; O, 8.65. Found: C, 82.41; H, 9.19; O, 8.69.

This reaction results in a mixture of two (**16a** and **16b**) diastereoisomers, epimeric around the C_{23} asymmetric carbon. Separation of these isomers proved to be difficult; nevertheless, we were able to obtain a pure sample of each by thin layer chromatography on fluorescent silica involving at least 12 successive elutions with pentane–ether (10:1). Subsequently, each isomer was recrystallized from methanol–ether. The least polar substance (**16a**) melted at 145–147° and the other (**16b**) at 146–148°. Owing to the closeness of the melting points, nmr spectra and optical rotations of the two isomers were also taken: nmr (**16a**) ($CDCl_3$) δ 0.65, 0.95 (singlets, C_{18} and C_{19} protons), 2.05 (singlet, acetoxy protons), 4.8 (multiplet, 2 H, proton α to carbonyl and 3β proton), 7.1–8.2 (10 H, multiplet, aromatic protons); nmr (**16b**) 0.5, 0.9 (singlet, C_{18} and C_{19} protons), 2.0 (singlet, acetoxy protons), 4.7 (2 H, multiplet, proton α to carbonyl and 3β proton), 7.1–8.2 (10 H, multiplet, aromatic proton); $[\alpha]D$ ($CHCl_3$) (**16a**), −33.5°; $[\alpha]D$ ($CHCl_3$) (**16b**), +76°.

3α-Acetoxy-20-methylene-5β-pregnane (17).—This compound was obtained by irradiation of a sample (1.8 g) of the ketone mixture **16**. A procedure identical with that described for the photolysis of compound **5** was followed, except that in the chromatography of the products a 10:1 pentane–ether mixture was used. Thus 450 mg (38%) of pure product were obtained which

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crystallized spontaneously. Recrystallization from methanol–ether at −10° afforded an analytical sample (mp 85–86.5°): ir (CS_2) 3080, 1740, 1240, and 885 cm^{-1}; nmr ($CDCl_3$) δ 0.55, 0.95, and 1.77 (singlets, C_{18}, C_{19}, and C_{21} protons), 2.05 (singlet, acetoxy protons), 4.62 and 4.75 (two adjacent singlets, exocyclic methylene and 3β protons); $[\alpha]D$ ($CHCl_3$) +41°.

Anal. Calcd for $C_{24}H_{38}O_2$: C, 80.39; H, 10.68; O, 8.92. Found: C, 80.56; H, 10.52; O, 8.75.

The above irradiation was repeated many times. The yields in *tert*-butyl alcohol ranged from 35 to 38% and in benzene from 33 to 35%.

Final confirmation was obtained by lithium aluminum hydride reduction of the acetoxy compound **17** followed by standard ozonolysis of the resulting alcohol **18**. Thus a sample of 3α-hydroxy-5β-pregnan-20-one (**19**) was obtained whose physical constants and spectra were identical with those of an authentic sample.[8]

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Registry No.—**1**, 2204-14-0; **2**, 42151-39-3; **3**, 42151-40-6; **4a**, 42151-41-7; **4b**, 42151-42-8; **5**, 42151-43-9; **7**, 145-13-1; **8**, 2415-36-3; **9**, 978-98-3; **10**, 18000-86-7; **11**, 42151-47-3; **12**, 4729-67-3; **13**, 1249-75-8; **14**, 42151-48-4; **15**, 4144-29-0; **16a**, 42151-50-8; **16b**, 42151-51-9; **17**, 42151-52-0.